

REMARKS

In the Office Action dated December 11, 2008, the Examiner: (1) rejected claims 75-76, 78-82, 85-86, 91-92, 94 -95 and 116-118 under 35 U.S.C. § 112, ¶ 1 as failing to comply with the written description requirement; (2) rejected claims 75-76, 78-82, 85-86, 91-92, 94-95 and 116-118 under 35 U.S.C. § 112, ¶ 1 as failing to comply with the enablement requirement; (3) rejected claim 75 under 35 U.S.C. § 112, ¶ 2 as being incomplete for omitting essential steps; (4) afforded a priority claim only to the immediate parent 09/088,820; and (5) rejected claims 75-76,78-82, 85, 86, 91-93, 95, 96-98, 102, 106-109 and 112-115 under 35 U.S.C. § 103(a) as being unpatentable over Nikiforov *et al.* (Nucleic Acids research, 1994, vol. 22, no. 20, p. 4167-4175) in view of Jeanpierre (Ann. Hum. Genet. (1992) 56:325-330).

On March 18, 2009 and April 10, 2009, the Examiner and the undersigned attorney of record conducted interviews in which they discussed the outstanding rejections. In view of those interviews, Applicants have amended the claim set as follows:

Claim 75 has been amended: (i) in step (A) to recite that the material that is analyzed is “from said biological sample” and what is produced is “a measure of” the intensity of the “first” allele specific quantitative signal; (ii) to add step (B), which parallels step (A), but produces a second reaction value that is “a measure of the intensity of a second allele-specific quantitative signal”; (iii) in step (C), to remove the term “establishing,” to recite a step of “calculating a set of probability distributions from a set of input data, wherein said set of input data is obtained under conditions that are comparable to the conditions under which the first reaction value and the second reaction value are obtained,” and to make subsection (C) both internally consistent and consistent with steps (A) and (B); (iv) in step (D), to add references to steps (A), (B) and (C); and (v) in step (E), to recite that the genotype is based on “the measure of conditional probability of step (D) of each genotype of interest at the locus for said subject.” Support for these amendments may, for example, be found within the claim itself, as well as in the specification at the following places: page 2, line 31 – page 3, line 6 (“Each probability

distribution associates a hypothetical pair of first and second reaction values with a single probability of each genotype of interest."); page 3, lines 6-17 (data for probability distributions may contain other reaction values that are obtained under conditions comparable to those under which the first and second reaction values are obtained); page 12, line 7- page 13, line 12 (input data obtained using comparable biochemistry and example of how to preprocess it); page 13, line 13 – page 14, line 9 (association of hypothetical input data and genotype to establish initial probability distributions); page 14, lines 14-16 (probability distributions may be fit to observed data); page 14, lines 18-20 (calculate the conditional probability of each genotype given a signal); page 16, lines 25-32 (fitting the probability distribution to the input data, by for example defining the probability of a signal point for a genotype to be a function of the distance between that point and the observed mean); page 18, line 22 – page 19, line 2 and Appendix A (example of fitting probability distributions).

Claim 76 has been amended to provide proper antecedent basis.

Claims 78-82 have been canceled.

Claim 85 has been amended to provide proper antecedent basis.

Claim 86 has been amended to provide proper antecedent basis and to depend on claim 75.

Claims 91 and 92 have been canceled.

Claim 94 has been amended to provide proper antecedent basis.

Claims 95 and 116 have been canceled.

Claim 117 has been amended to depend on claim 75 and to provide proper antecedent basis.

Claim 118 has been canceled.

Support for new claims 119 and 120, may, for example, be found in the language of previously pending claim 75 as well as in figure 2.

Support for new claim 121 may, for example, be found on page 8, lines 12-16.

Support for new claim 122 may, for example, be found on page 2, lines 16-17 and lines 29-31.

New claim 123 is an independent claim, and new claims 124-132 depend on new claim 123. Support for new claim 123 may, for example, be found in passages in which the features of claim 75 that are cited above find support, previously pending claim 75 and on page 3, lines 21-31 (initial probability distributions may be estimated, then used to determine initial genotype probabilities to obtain data that is used to modify the initial probability distributions); page 7, lines 25-29 (calculating initial probability distributions); page 7, line 30 – page 8, line 5 (use initial probability distribution to determine initial conditional probability); page 8, lines 5-8 (modify initial probability distribution); page 15, lines 20-26 (computed genotypes used to refit the distributions).

Support for new claim 124 may, for example, be found on page 15, lines 29-32.

Support for new claims 125 and 126 may, for example, be found on page 18, lines 23-27.

Support for new claim 127 may, for example, be found on page 15, lines 6-15.

Support for new claim 128 may, for example, be found on page 15, lines 24-26.

Support for new claim 129 may, for example, be found on page 2, lines 16-17 and lines 29-31.

Support for new claim 130 may, for example, be found on page 8, lines 12-16.

Support for new claims 131 and 132 may, for example, be found in the language of previously pending claim 75, as well as in figure 2.

New claim 133 is an independent claim, and new claims 134-139 depend on new claim 133. Support for new claim 133 may, for example, be found in passages in which as noted above the features for claims 75 and 123 are found, as well as on page 17, lines 5-14 and page 17, line 28 – page 18, line 16 (using an initial genotype guess and initial guess variation).

Support for new claim 134 may, for example, be found on page 2, lines 16-17 and lines 29-31.

Support for new claim 135 may, for example, be found on page 15, lines 21-32.

Support for new claim 136 may for example, be found on page 17, lines 5-7.

Support for new claim 137 may, for example, be found on page 17, lines 13-14.

Support for new claims 138 and 139 may, for example, be found in the language of previously pending claim 75, as well as in figure 2.

In view of the amendments above, Applicants respond to the issues raised by the Examiner as follows:

1. Response to rejection of claims under 35 U.S.C. § 112, ¶ 1 as failing to comply with the written description requirement

The Examiner rejected the previously pending claim set under 35 U.S.C. § 112, ¶ 1 as failing to comply with the written description requirement. The Examiner raised the following issues with respect to the written description requirement: (i) “First the determination of the reaction value is described only generally, except for an embodiment comprising genetic bit analysis, which is described in some greater detail”; (ii) “regarding the process of establishing a set of probability distributions, the specification does not provide sufficient guidance or detail regarding how these probability distributions are established”; and (iii) “reading the specification in light of the claims, it is unclear if the conditional probability measure is used to assign an entirely unknown genotype based on a data set or if the conditional probability is used to confirm a genotype that has been measured previously.” Applicants respond to each of these issues as follows:

First, the Examiner states that the determination of the reaction value is described only generally, except for an embodiment comprising genetic bit analysis. Applicants respectfully disagree and submit that they have provided a sufficient description of the determination of the reaction value. As the specification recites, the production of a reaction value refers to the production of a physical state that is quantifiable as a reaction value that is indicative of a given allele. (Page 5, lines 9-11 and 25-30; page 6, lines 17-21; page 8, lines 9-12) Thus, the specification provides a sufficient description of the determination of a reaction value, and should not be limited to GBA.

Moreover, the specification notes that in addition to the generation of reaction values through GBA, “the present invention is also applicable to other reaction systems

for allele determination, such as allele-specific hybridization (ASH), sequencing by hybridization (CBH), oligonucleotide ligase assay (OLA), and allele-specific amplification, using either the ligase chain reaction (LCR) or the polymerase chain reaction (PCR)" (page 4, lines 23-28) and "the invention may be applied to GBA, OLA, ASH and RAPD-type markers" (page 10, lines 16-18). Each of these techniques was well known in the art at the time of Applicants' invention. Accordingly, Applicants submit that the specification identifies a number of techniques in which a reaction value is generated and the identification of these techniques provides support for the claimed features for reacting a material to produce a reaction value regardless of whether performed in conjunction with GBA.

Second, the Examiner asserted that the specification does not provide sufficient guidance or detail regarding how the probability distributions are established. Applicants have amended step (C) of claim 75 to remove the term "establishing" and instead to recite "calculating a set of probability distributions from a set of input data, wherein said set of input data is obtained under conditions that are comparable to the conditions under which the first reaction value and the second reaction value are obtained." Applicants submit that the calculation of a set of probability distributions from a set of input data is well within the skill of a person of ordinary skill in the art. Moreover, the specification identifies a number of ways in which a probability distribution may be obtained, including using a best fit methodology (page 14, lines 14-17; page 15, lines 20-28; page 16, lines 25-32; page 17, line 28 – page 19, line 16) or using a predefined fixed distribution (page 14 lines 14-15). By way of example, figure 3 shows a set of data and figures 4-6 show representations of distributions for three genotypes of interest as calculated by the code in Appendix A. Thus, the specification provides ample detail of how the probability distributions may be established.

The Examiner acknowledges the equations that are on page 13 of the specification but asserts "the specification is not clear about how these equations are used to establish probability distributions, how the hypothetical reaction values are established, or how the two are translated into conditional probability determinations. . . . Without more details

or raw data used in the calculations which demonstrates how a data point is converted into a probability distribution or is modified by the distribution as required by steps C and D of claim 75, it is not clear from a reading of the specification how to practice the invention.” Applicants respectfully disagree with the Examiner’s statements, but have amended claim 75 to make explicit what was implicit, and in light of these amendments Applicants submit that these rejections are moot.

More specifically, Applicants have recited in step (C) that the set of probability distributions are calculated from a set of input data that is obtained under conditions that are comparable to the conditions under which the first and second reaction values are obtained. This set of probability distributions may be the distributions that are referred to as the “initial probability distributions” on page 13, lines 14-30 of the specification. In the simplest terms, it provides the conditional probability of a pair of signals, given a particular genotype. As recited in claim 75, this set of initial probability distributions do not need to be created with the first and second reaction values that are measured in steps (A) and (B). Thus, whereas steps (A) and (B) refer to the empirically measured first and second reaction values, step (C) refers to the hypothetical reaction values that are associated with a probability of a genotype given the input data.

Further, in step (D) there is a second conditional probability. Whereas the conditional probability distribution of step (C) is a measure of the probability of pair of signals given a genotype and is calculated based on the input data of step (C), the conditional probability of step (D) is a measure of the likelihood of a genotype, given actually measured reaction values from steps (A) and (B). Thus, claim 75 does not require that the probability distributions of (C) be modified.

Third, the Examiner wrote “it is unclear if the conditional probability measure is used to assign an entirely unknown genotype based on a data set or if the conditional probability is used to confirm a genotype that has been previously measured.” (page 5 of Office Action) The Examiner indicated that this issue was raised because the results of the first step of the method of claim 75 lead to data that was organized in view of a previously measured genotype. She then contrasted what was claimed with the claimed

result of claim 86. Applicants have amended claim 75 to recite that the genotype that is determined in step (E) is based on the conditional probability of step (D). In view of this amendment, Applicants submit that the claim explicitly notes that the genotype that is determined can be used to assign an entirely unknown genotype.

Additionally, because the Examiner raised a concern about the relationship between claims 75 and 86, Applicants note that claim 86 includes the additional step of calculating a confidence score and determining whether a significant downward trend in confidence scores has occurred. Thus, whereas claim 75 is directed to a method that determines the genotype based on the highest probability among the possible genotypes, in the method of claim 86, one also analyzes the confidence score, which is a measurement of the likelihood that the determination of the genotype was correct, and determines whether there has been a significant downward trend in confidence scores. With respect to the Examiner's reference to claim 118, Applicants note that this claim has been canceled.

The above-referenced points were made with respect to independent claim 75. Because based on the foregoing, independent claim 75 complies with the written description requirement, Applicants request that the rejection be withdrawn with respect to the claims that depend on it as well.

With respect to new independent claims 123 and 133 and the claims that depend on them, Applicants submit that for the same reasons that independent claim 75 complies with the written description requirement, and in view of the portions of the specification cited above, these claims comply with the written description requirement as well.

2. Response to rejection under 35 U.S.C. § 112, ¶ 1 as failing to comply with the enablement requirement

The Examiner rejected the previously pending claim set under 35 U.S.C. § 112, ¶1 as failing to comply with the enablement requirement. The Examiner raised the following points with respect to this issue: (i) the specification does not teach how to obtain a reaction value other than in the most general terms; and (ii) the specification

does not teach how the distribution set of probability distributions are established or where the hypothetical reaction values are obtained. Applicants respond to each of these issues.

First, as with the rejection for alleged failure to comply with the written description requirement, the Examiner asserts that the determination of the reaction value is described generally except for with respect to GBA. As Applicants noted above, they disagree. The specification specifically discloses other methods for obtaining reaction values, including ASH, CBH, OLA, and allele specific amplification, (see page 4, lines 23 -28; page 10, lines 15-18), and describes exemplary instrumentalities for implementing ways to measure a reaction value, including an optical transducer, an optical detector, and a bichromatic microplate reader from ICN Biomedical (see page 7, lines 20-24; page 11, lines 11-31). Because the ability to measure reaction values in the applications described above was well within the scope of the knowledge of persons of ordinary skill in the art, Applicants request that this basis for rejection be withdrawn.

Second, the Examiner asserted that it is unclear how the probability distributions are established. As Applicants noted above, they have removed the term “establishing” from claim 75 and instead, the method describes calculating the probability distributions from input data. Thus, the source of the data is not significant, so long as it is obtained under conditions that are comparable to the conditions under which the first reaction value and second reaction value are obtained. With respect to how to calculate the set of probability distributions, Applicants submit that how to calculate a set of probability distributions given a set of data is well within the skill of a person of ordinary skill in the art.

Moreover, the present application provides examples of how to calculate a probability distribution. For example, the specification describes that a probability distribution: may be fit to observed data, where a conditional probability of a signal point for some genotype may be defined as a function of the distance between that point and the observed mean for that signal (page 14, line 15 and page 16, lines 25-32); may be fit to assumed genotypes in an iterative adaptive fitting algorithm, such as Estimation-

Maximization (page 14, lines 15-17 and page 15, line 20-page 16, line 8); and may be fit to initial genotype guesses produced from a simple or heuristic algorithm (page 17, lines 5-14). An example of the calculation of a probability distribution may also be seen in Appendix A.

3. Response to rejection under 35 U.S.C. § 112, ¶2 as being incomplete for omitting essential steps

The Examiner rejected claim 75 for being incomplete for omitting essential steps because the claim is allegedly directed to only reacting the material at a first locus to produce a first reaction value. Applicants respectfully disagree with the rejection, but in the interest of furthering prosecution have amended claim 75 to include a step of reacting the material at the locus to generate a second reaction value. In view of this amendment, Applicants request that this rejection be withdrawn.

4. Response to award of priority claim

The Examiner awarded Applicants a priority claim only to the immediate parent 09/088,820 (the “‘820 application”). Applicants request that in view of the amendments above, the Examiner revisit the priority claim and award priority to the pending claims to U.S. Application Serial No. 08/362,266 (the “‘266 application”), which is now U.S. Patent No. 5,762,876, and U.S. Application Serial No. 08/173,173, filed December 23, 1993 (the “‘173 application”).

Applicants note that the present application was filed as a continuation of the ‘820 application, which was filed as a continuation of the ‘266 application. Accordingly, Applicants ask the Examiner to clarify why she believes that the present application is not entitled to priority to at least the ‘266 application.

Additionally, although the ‘266 application is a continuation in part application of the ‘173 application, Applicants submit that support for the present claims fully exists in the ‘173 application. Applicants direct the Examiner to the following portions of the ‘173 application as disclosing the relevant claim features:

Applicants: Lincoln, *et al.*

Serial No.: 09/618,178

Filing Date: July 18, 2000

Amendment and Response to Non-Final Office Action dated December 11, 2008

Page 21 of 24

- A method of determining the genotype at a locus within genetic material obtained from a biological sample. (page 1, lines 30-32; page 4, lines 19-21 of the '173 application)
- Reacting the material to produce a first reaction value. (page 1, lines 33-35 of the '173 application)
- Reacting the material to produce a second reaction value. (page 2, lines 8-11 of the '173 application)
- Data set includes other reaction values obtained under conditions comparable to those under which the first and second reactions are run. (page 2, lines 24-30; page 8, lines 13-26)
- Simple or heuristic algorithms may be used to produce an initial genotype guess for each input data point. (page 12, lines 3-5 of the '173 application)
- Establishing probability distributions that associate hypothetical reaction values with corresponding probabilities. (page 2, lines 13-16; page 4, lines 11-15; page 8, line 27 – page 10, line 6; page 12, lines 13-24 of the '173 application)
- Normalizing data and fitting probability distributions. (page 11, line 28-page 12, line 2; page 12, line 24-page 13, line 3; page 13, lines 9-18 of the '173 application)
- Probability distribution may be estimated. (page 2, lines 32-34 of the '173 application)
- Applying reaction value to each pertinent probability distribution. (page 4, lines 15-19; page 5, lines 10-14 of the '173 application)
- Compute the conditional probability of each genotype. (page 10, lines 7-17 of the '173 application)
- Determine the genotype. (page 10, lines 18-27 of the '173 application)
- Determine the confidence score. (page 10, lines 18-27 of the '173 application)

- Resulting data may be used to modify initial distributions. (page 2, line 37- page 3, line 5; page 11, lines 1-19 of the '173 application)
- Assign initial probability distributions to the data set that would associate hypothetical reaction values with corresponding probabilities for each genotype of interest. (page 5, lines 22-26 of the '173 application)
- Use initial probability distribution to determine initial conditional probabilities. (page 5, lines 26-30 of the '173 application)
- Modify initial probability distribution. (page 5, lines 30-33)
- Allele may be a single specific nucleotide. (page 3, lines 11-12; page 3, lines 25-27 of the '173 application)
- Other reaction systems: allele-specific hybridization (ASH), oligonucleotide ligase assay (OLA), and allele-specific amplification, using either the ligase chain reaction (LCR) or the polymerase chain reaction (PCR) (page 3, lines 15-18 of the '173 application)
- Optical transducer and optical detector, including example from ICN Biomedical. (page 5, lines 18-19; page 7, lines 28-34 of the '173 application)

Pursuant to MPEP 201.11[G], Applicants submit that upon issuance of the pending claims, the patent term should be measured from the filing date of the '173 application, which was filed on December 23, 1993. Upon agreement of the Examiner and the Applicants to the correct priority claim, Applicants shall submit a Supplemental Application Data Sheet and request the issuance of an updated filing receipt.

5. Response to Rejection under 35 U.S.C. § 103(a)

The Examiner rejected the previously pending claim set as being unpatentable over Nikiforov in view of Jeanpierre. For at least the two reasons that follow, Applicants submit that the rejection is improper.

First, Nikiforov is not prior art. As noted above, for the pending claims Applicants are entitled to claim priority to U.S. Patent Application Serial No. 08/173,173,

which was filed on December 23, 1993. Nikiforov has a publication date of no earlier than 1994. Therefore, Nikiforov was filed after Applicants' earliest effect filing date, and it is not prior art. Accordingly, Applicants submit that the rejection that is based on the combination of Nikiforov with another reference is improper and should be withdrawn.

Second, Applicants submit that even if the Examiner were to maintain that Nikiforov is prior art, the combination of Nikiforov with Jeanpierre was improper. Nikiforov is directed to a method for typing single nucleotide polymorphisms. (See Abstract of Nikiforov) It focuses on the biochemical features of the methods described therein. (page 4168 of Nikiforov "In this paper we focus on the biochemical basis of GBA.") As the Examiner notes on page 17 of the Office Action, Nikiforov does not teach establishing a distribution set of probabilities or analyzing conditional probabilities.

Jeanpierre is directed to a method for providing the likelihood of a genotype of an unsampled individual when information about the genotype of the individual's relatives is known. (Jeanpierre Abstract) Accordingly, Jeanpierre focuses on examining known genotypes in a pedigree to predict the genotype of the unsampled individual. That reference does not concern itself with experimentally obtaining information from a biological sample of a subject. In fact, Jeanpierre suggests a method that may be of use precisely when there is no access to a biological sample that contains the genetic material of interest. (See Jeanpierre Summary p. 325 "The likelihood of a genotype of an unsampled individual.")

Thus, Jeanpierre and Nikiforov provide answers to different questions that are applicable in mutually exclusive circumstances. In Nikiforov, one has a sample to test, the genotype of which is not known, and asks what is the genotype of that sample based on the results of direct probing of that sample? By contrast, in Jeanpierre there must be an absence of a sample (or person) to test, and one asks, what is the genotype of the person of interest, based on the known results of information from persons other than the person of interest? If the person of interest is present, then one has no use for the methodology of Jeanpierre, and if the person is absent, one cannot use the empirical testing methods of Nikiforov. Therefore, a person of ordinary skill in the art would not combine these

references.

Additionally, even if a person were to combine these references, he or she would not reach the claimed invention. If one were to apply the GBA testing methods of Nikiforov to samples from the persons who were available in Jeanpierre, one would at most obtain experimental testing results for the relatives of the person of interest and not for the person of interest. This would not provide a conditional probability of a genotype based on the experimental testing of the sample of interest as is required by the pending claims. Thus, even if one were to combine the two cited references, one would not obtain the claimed invention.

Based on the foregoing, Applicants request that all outstanding rejections be withdrawn.

In addition to the fee for the petition for extension of time, Applicants authorize payment of all fees in connection with the additional seven claims over twenty that have been added. If any further fees are due, please charge Deposit Account No. 11-0171 for such sum.

Respectfully submitted,

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